Chapter 11
Quality of Life Assessments in the Development and Clinical Trials of New Antipsychotics: Pharmaceutical Industry Perspective

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11.1 Introduction

For more than 50 years, pharmacotherapy of schizophrenia has focused primarily on the treatment of positive symptoms (i.e., hallucinations, delusions, excitement, and hostility) and on the prevention of exacerbations and re-hospitalizations (maintenance treatment). The aspect of quality of life (QoL) has only recently found to be critical for clinical trials in patients with severe mental disorders and important as a target for therapeutic interventions, in spite of the fact that schizophrenia is associated with significant reductions in QoL. Historical milestones for the introduction of quality of life into mental health can be found in a paper by Bobes and Gonzales (1997).

Clinical practice has had little influence on QoL as shown in a clinical study following patients over 10 years. Poor outcomes were found in 76 % of the patients, and only 24 % reported that they had improved or remained satisfied with their QoL (Ritsner et al. 2012). Now an increasing number of trials also include quality of life assessments, although in most cases still only as secondary or exploratory outcome parameters. Results from these trials are often difficult to interpret due to a number of methodological shortcomings. This may also have contributed to the fact that quality of life measures have not yet made a large impact on clinical care (Awad and Voruganti 2012).

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11.2 Methodological Aspects of Quality of Life Assessments in Drug Development Trials

There is no universally accepted operational definition of quality of life and various authors have proposed different concepts. This lack of consensus is a major problem for research and has a serious impact on the assessment of QoL in the context of drug development. However, there appears to be general agreement that QoL is primarily subjective in nature and represents the patient's personal view or feelings ("well-being," "happiness," or "life satisfaction") but also has important objective facets related to the environment and to social functioning. QoL assessments therefore cover several dimensions like the patients' overall functioning, their psychological well-being, their perceived quality of life, and the impact of the environment on their quality of life.

11.2.1 Selection of Assessment Instruments

Since there is no "gold standard" instrument for the assessment of QoL, the selection of one or more specific QoL measurements for use in a clinical trial will depend on the type of questions that are to be addressed. Investigators, who design a trial, should be familiar with the theoretical construct that the authors of a particular instrument have applied and with results from the use in situations similar to the intended research. In general, measurements should have documented adequate psychometric properties in the particular populations for which they will be used. As an example, reliability data established in chronic stable outpatients may not be extrapolated to acutely exacerbated hospitalized patients.

Social and environmental factors are critical for QoL; however, they are not targets for interventions in clinical trials where the emphasis is mainly on health and illness. The FDA 2009 Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims discusses quality of life and explains in the glossary: Quality of life is "a general concept that implies an evaluation of the effect of all aspects of life on general well-being. Because this term implies the evaluation of non-health-related aspects of life, and because the term generally is accepted to mean *what the patient thinks it is*, it is too general and undefined to be considered appropriate for a medical product claim." However, the FDA accepts claims based on health-related quality of life (HRQL) which the agency defines as follows: "HRQL is a multi-domain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life."

Assessment of QoL or HRQL in mental disorders is faced with several methodological challenges, not least due to the fact that QoL to a large extent involves psychological aspects. As a consequence, there may be an overlap between items that are directly linked to psychopathology and those that are assessed in the context of QoL, like depressed mood, anxiety, somatic concerns, sleep disturbances, and

pain – to name only a few. On the other hand, mental states like depression, dysphoria or euphoria, as well as cognitive impairment may lead to bias in subjective assessment, over- or underestimating the level of QoL. Measurements based on "subjective" patient-reported QoL have been accepted in conditions like cancer or chronic pulmonary diseases but have been met with skepticism in the case of schizophrenia (and even depression), since there were doubts whether patients could provide reliable and valid information on their QoL.

There are several instruments with a particular focus on health-related quality of life (HRQL) covering important general domains like physical health, mental health, cognitive functioning, sexual functioning, and role performance in work or school. The SF-36 (Ware and Sherbourne 1992), a generic QoL measure, contains 36 items which are grouped into 8 scales. These are physical functioning, role physical, bodily pain, general health, vitality, social functioning, and role emotional and mental health; they can be summarized into two broad dimensions, physical health and mental health. The instrument has been widely used in various physical illnesses but also in depression and schizophrenia (Nasrallah et al. 2004). The scale differentiated between patients with schizophrenia and healthy controls and showed improvements in patients with schizophrenia from admission to discharge (Pukrop et al. 2003). Several other generic scales that have been used in samples with schizophrenia, like the WHOQoL (The Whoqol Group 1998) and the EQ-5D (Brooks et al. 2013), are discussed by Bobes and colleagues (2005), who summarize findings supporting their use as the two instruments discriminated between patients with schizophrenia and healthy subjects and showed that higher severity was related to lower QoL scores. Generic instruments can be used for cost-utility analysis since they can refer to sets of preference-based utility values and may allow for comparisons across diseases, but will not necessarily capture all important aspects of a specific condition. Furthermore, it remains questionable whether similar scores on a generic instrument have the same meaning and relevance in different diseases like pulmonary disease, cancer, diabetes, or schizophrenia.

For this reason specific instruments have been developed for use in schizophrenia. Initially, mainly "objective" clinician-rated instruments were applied, like the QLS (Heinrichs et al. 1984). This scale has been widely used, but it was originally intended for the assessment of a deficit syndrome and as such rather measures the impact of negative symptoms. Several other clinician-administered instruments also exist, like the Quality of Life Interview, QoLI (Lehman et al. 1982), and the Lancashire Quality of Life Profile, LQoLP (Oliver et al. 1996).

Like healthy subjects, psychiatric patients can be prone to various reporting biases known also as "social desirability." In spite of these potential limitations in assessments, a number of studies (e.g., Wehmeier et al. 2007) have provided empirical evidence demonstrating that a vast majority of patients with schizophrenia, particularly chronic stable and treatment-adherent patients with moderate severity, can in fact reliably assess their QoL and that tools based on self-reports are useful in clinical trials and outcome studies. However, patients with acute exacerbations, severe psychotic symptoms or hostility, profound lack of insight, or substantial cognitive impairment may be unable to fill in self-reports or to respond adequately to a QoL interview.

Several patient-rated instruments for schizophrenia are now available, including the Schizophrenia Quality of Life Scale (SQLS) (Wilkinson et al. 2000), the Sevilla Quality of Life Questionnaire (Ibáñez et al. 1997), the Personal Evaluation of Transitions in Treatment (PETiT) (Voruganti and Awad 2002), and the Auquier Schizophrenia Quality of Life Questionnaire S-QoL (Auquier et al. 2003). None of these instruments have so far been widely used in clinical trials so that there is only limited experience with their ability to measure treatment effects. Bobes et al. (2005) discuss several instruments, which are all based on different theoretical approaches and dimensions, contain between 21 and 143 items, and take between 2 and 45 min to complete: QLS, clinician-rated only with focus on deficit syndrome; QoLI and LoLP, patient-rated, based on a general QoL model; SQLQ, patient-rated favorable and unfavorable aspects of life; PETiT, patient-rated changes of symptoms, side effect, and performance during treatment; and the S-QoL, patient-rated with focus on discrepancies between their expectations and their current experiences. The authors conclude that the choice of the most appropriate instrument depends on the aim of the research and that generic and specific instruments should be combined.

A scale worth mentioning, which has demonstrated sensitivity to change and assesses side effects of antipsychotic treatment rather than the impact of schizophrenia per se on QoL, is the Subjective Well-Being Under Neuroleptic Scale (SWN) (Naber 1995). With regard to a broader concept of well-being, Schrank et al. (2013) comment that this is still "ill-defined" although it has conceptual overlaps with HRQL. It depends on the environment, the economy, relationships and family connections, activities, finances, general and mental health, as well as satisfaction.

At present there is not one single "optimal" instrument for the "objective" or "subjective" assessment of QoL that would be useful for all kinds of clinical trials. In fact, a selection of several instruments adapted to the research aim may provide a better fit. However, discrepancies between results from "objective" clinician-rated measures of QoL and from "subjective" patient-rated rated measures have been observed and may be explained by the fact that instruments are based on different constructs and tap into different domains. Patients and clinicians also appear to differ in their valuation of aspects like symptom profile, adverse events, living situation, and role functioning. Thus it is unclear if and how well objective and subjective measures should correlate. According to Wehmeier et al. (2007), QoL is perceived more similarly by clinicians and patients in more severely ill patients, in patients with lack of tolerability or in need of a treatment change, in younger patients, and in patients who have received psychotherapy; on the other hand, QoL in women with schizophrenia was rated higher by clinicians than by the patients themselves. In fact, there have been observations that self-rated benefits of treatment have not been captured by clinician-rated measures (Awad and Voruganti 2004). Since QoL in the case of schizophrenia is also essentially a subjective construct, assessments should always include subjective, self-report-based assessments as well as objective measures.

11.2.2 Factors with Potential Impact on Quality of Life Assessments in Clinical Trials with Antipsychotics

Clinical development programs are increasingly conducted on a global scale. However, the relevance of diverse cultural backgrounds for the assessment of QoL in schizophrenia in multinational clinical trials has not been systematically explored in the literature. The World Health Organization (WHO) has made an effort to develop methods that are acceptable across various cultures based on the idea that QoL is what individuals perceive as their position in life related to their goals and values. In a review of health-related quality of life measures in Arabic-speaking populations, Al Sayah et al. (2013) pointed out that most instruments have originally been developed in the English language for a specific culture and that cross-cultural adaptation techniques are needed to preserve aspects of equivalence when comparing populations from different geographical regions. On a similar note, Xiang et al. (2010) reviewed the literature on trials with Chinese patients with schizophrenia and concluded that cultural factors play an important role and that assessment tools derived from Western sources may not have sufficient sensitivity to eliminate cultural bias.

Ratings of QoL may be influenced by several other factors unrelated to treatment, like demographics, education, social status, living conditions, employment status, psychopathology, and comorbidity – to name just some. These factors and their potential interactions with treatment also need to be taken into consideration when designing trials and selecting populations in order to correctly interpret the potential impact of treatment effects on QoL measures.

In general, younger patients, women, married persons, those with lower levels of education, and patients participating in support programs or psychotherapy report better quality of life. Negative correlations with QoL are reported for duration of illness, duration of untreated psychosis, and levels of negative and depressive symptoms (Bobes et al. (2005). Caron et al. (2005) reviewed the literature on sociodemographic and clinical predictors for various QoL domains in schizophrenia. Higher age (i.e., 40–49 years) was related to better QoL. Women reported higher QoL total scores and better QoL related to activities of daily living. The relation between the level of education and QoL may not always be straightforward. Although in general patients with higher education levels report higher degrees of satisfaction with life and psychological well-being, there are some patients with an inverse relation between higher education and higher premorbid social status and reported satisfaction, possibly due to an illness-related downward shift in status.

There is still limited data on the relevance for QoL of factors like employment status, ability to work, income, and social relations, legal problems, and premorbid adjustment and results vary between samples. Homeless people with schizophrenia generally report low QoL except when showing significant lack of insight or neurocognitive impairment. Nilsson and Levander (1998) found no subjective differences in quality of life discontent scores among four other living conditions (mental hospital, group home, treatment collective, and patients' own flats). Although the four

groups had relevant differences in psychopathology, the finding could indicate that patients felt that their personal needs were adequately met in the respective institutions.

Several specific clinical variables have been consistently found to have an impact on QoL ratings – although the degrees varied between studies. Lower QoL is associated with the level of depression and negative symptoms, although there could be an overlap in measures of QoL with negative symptoms since both tap into the same construct, as is the case with the QLS, originally developed to assess deficit schizophrenia. Negative symptoms may explain up to 45 % of the variance in QoL in stable patients but only around 15 % during acute exacerbations (Bow-Thomas et al. 1999). Negative symptoms are usually present to a significant extent in acutely exacerbated patients, but the severity of positive symptoms may overshadow the clinical picture. Hayhurst et al. (2014) identified depression as the main driver for patient-rated reduced QoL whereas negative symptoms were the main driver for clinician-rated low QoL. Unsurprisingly, lack of insight was the main driver for discrepancies between clinician- and patient-rated QoL assessments. The role of positive symptoms for QoL is less clear. Most authors have found no strong relation between positive symptoms and QoL, although there are some reports that see them as predominant factors for QoL. In a meta-analysis Eack and Newhill (2007) reported that positive and negative symptoms were significantly negatively related to both composite and domain-specific indicators of QoL, although the relationships between positive symptoms and QoL were not particularly strong, except for health-related QoL. General psychopathology, which includes symptoms like depression and anxiety, was significantly negatively related to QoL. The lack of a uniform relation between positive symptoms and QoL can also be seen in a paper by Xiang et al. (2012) who reported on a sample of community-dwelling Chinese patients with schizophrenia. More severe positive symptoms predicted worse QoL in psychological and environmental domains and better social support independently predicted higher QoL in all domains. Overall psychopathology predicted both worse physical and psychological domains; depressive symptoms and being married predicted worse physical and social QoL, respectively.

The level of insight and cognitive impairment are of specific importance as they may introduce biases into ratings and reduce their reliability. This may be the case in patients with severe symptomatology and during acute exacerbations. As an example, Siu et al. (2015 in press) showed that the level of insight and cognitive performance had moderating effects on the reported level of subjective life satisfaction.

Some general factors related to treatment have also been found to have an impact on QoL. A recent hospitalization during the previous 12 months is associated with lower QoL although this could also be an indirect effect of higher severity or a less favorable course of the illness. Patients with longer duration of the illness may report increased quality of life, possibly due to better adjustment to treatment or greater autonomy. There appears to be an interaction between treatment adherence and QoL. Those with higher QoL are more adherent, and those with better adherence report higher QoL and subjective well-being. Finally the quality of the patient-doctor relationship is directly related to QoL.

A general model linking clinical variables with health-related quality of life has been proposed by Wilson and Cleary (1995). Based on a classification scheme for different measures of health outcome, divided into five levels (biological factors, symptoms, functioning, general health perception, and overall quality of life), the authors suggest to analyze the causal relationships between them and to determine the size of their effects on outcome with statistical tools. Being able to identify how symptomatology, functional status, and other domains are interrelated may help with the interpretation of the observed effects of therapeutics on QoL measures. Several authors have attempted to develop a concept for QoL in schizophrenia. In their paper Awad et al. (1997) proposed and tested an integrative model, where QoL in schizophrenia is seen as the subject's perception of the outcome of an interaction between three major determinants: the severity of psychotic symptoms, side effects including subjective responses to antipsychotic drugs, and the level of psychosocial performance. This may be modulated by other factors like personality and premorbid adjustment that influence the outcome. In a cross-sectional study, the symptoms of schizophrenia, assessed with the Positive and Negative Syndrome Scale (PANSS), and the subjective distress due to adverse events like akathisia and neuroleptic dysphoria were found to explain nearly half of the variance in QoL in this population of stable patients. Ritsner and colleagues (2000) translated findings from several HRQL studies into a Distress/Protection Vulnerability model, which postulated dissatisfaction with HRQL as a particular syndrome linked to severe mental disorders, like schizophrenia. This syndrome was the result of an interaction between distressing factors and factors protecting against stress. The level of dissatisfaction with quality of life increases when distressing factors overweigh protective factors.

The ways how antipsychotic medications interact with QoL have been debated over time. Awad and Voruganti (2004) postulated that medications by themselves cannot raise the level of QoL in patients with schizophrenia; this would also require other interventions, such as rehabilitation or psychosocial skills training. However, several studies have now shown that QoL can actually improve during treatment with antipsychotics although the exact mechanism by which this is achieved is not clear and may actually differ between drugs and from trial to trial. As an example, Phillips et al. (2006) reported on significant correlations between changes in PANSS scores and changes on the SF-36 as well as on the QLS. In their sample there were a 30.72 % improvement on the PANSS total score and a 28.55 % improvement on the QLS total score.

In a meta-analysis paper, Leucht et al. (2009a) report differences between first- and second-generation antipsychotic effects on quality of life based, however, on merely 17 studies. For most compounds (amisulpride, aripiprazole, clozapine, sertindole, ziprasidone, and zotepine), the authors could actually only rely on one study with sample sizes between 72 and 311 subjects. For olanzapine there were 5 studies with a total of 1450 patients included, for risperidone 4 studies with a total of 330 patients, and for quetiapine 2 studies with a total of 166 patients. Only amisulpride, clozapine, and sertindole were better than the comparators on QoL measures with effect sizes between −0.24 and −0.44 (Hedges' g), but these results were based on a single trial and neither the specific measures of quality of life, nor

the effects of the first-generation comparators on these measures were discussed in detail in the paper.

Antipsychotic medications can cause a wide range of adverse events that may negatively affect QoL, especially when assessed with subject, patient-rated instruments. Still, the amount of variance in QoL explained by adverse events appears to be relatively small. In a multiple regression analysis, the amount of variance in QoL ratings explained was 20.9 % for psychosocial factors, 10.1 % for clinical symptoms and associated distress, and only 3.2 % for adverse effects (Ritsner et al. 2002).

The results are particularly contradictory when looking at extrapyramidal symptoms (EPS), a potentially major differentiator between typical and atypical antipsychotics. Two large effectiveness trials, CATIE (Swartz et al. 2007) and CUtLASS (Jones et al. 2006) found no differences in QoL between the two types of antipsychotics in spite of differences in the AE profiles. This could be due to methodological limitations in the two trials, as several other controlled studies and effectiveness trials have reported on better QoL outcomes with atypical antipsychotics, when assessed by subjective instruments (Naber and Lambert 2009). The total adverse event load also appears to be correlated with QoL as well as some individual adverse events like sexual side effects, sleep disturbances, tachycardia, dizziness, and fatigue. On the other hand, metabolic syndrome and weight gain have not been consistently identified as a source of reduced QoL.

There have been suggestions that improvement in QoL takes longer than symptomatic improvement. However, in a 12-week study to assess the effects of early response to an antipsychotic, Kinon et al. (2010) found that patients with an early improvement in their psychiatric symptoms also showed an early and consistent improvement in functioning, quality of life (QLS), and subjective well-being (SWN-K). This is of great relevance since early improvement in symptoms and in QoL has an important impact on long-term QoL (Karow et al. 2014). In this context it is important to assess how much change is actually needed to represent a "detectable change" in QoL. A clinician rating of "improved" appears to correspond to a 21 % decrease in PANSS score and to a 26 % increase of the QLS score. A rating of "much better" corresponds to a 45 % decrease of the PANSS total score and a 50 % increase on the QLS (Cramer et al. 2001). This information may also be useful for sample size calculations in order to ensure not only statistical significance but also clinical relevance and to identify "responder rates" which can then be used to calculate "numbers needed to treat" (NNT). In general, it is desirable to refer to a defined "minimal clinically important difference" (MCID) for a given QoL scale which can be derived either from a distribution-based method or from an anchor-based method described in detail by McLeod et al. (2011) and shown for the QLS by Falissard et al. (2015).

Besides the effects of treatment on QoL, the final outcome in a therapeutic trial most likely depends on additional factors and their interactions. These factors are, among others, the clinical features, adverse events and the distress they cause, distress-protective factors, the quality of the therapeutic relation, and elements of psychosocial support.

11.2.3 Clinical Trials with Focus on Quality of Life

As is the case for clinical research in general, there are several design features that also apply to clinical trials which focus on QoL. Assessments of QoL can be included in a wide variety of studies, ranging from cross-sectional and observational studies that investigate characteristics of relevant patient populations or current standards of care and patients' needs to naturalistic and interventional trials of various durations that provide comparative data for different drugs or interventions. The target audiences for these trials are clinicians, Health Technology Assessment (HTA) bodies, and regulatory agencies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). So far most studies are sponsored by the pharmaceutical industry; however, there have been calls for more independent, well-designed, and adequately powered, comparative, controlled studies.

In all cases, assessment tools should be chosen carefully with regard to their psychometric properties and corresponding to aim and design of the trial. When used in multinational trials, not only translations but also cultural adaptions may be needed to allow for valid comparisons, interpretation of the results, or pooling of the data. Trials should have adequate sample sizes and sample size calculations should take into consideration the reliability of the chosen instruments.

When there is more than one primary end point, the sample size needs to be adjusted for multiplicity. Underpowering should be avoided in comparative studies since it could lead to false conclusions about a lack of difference while there is actually just a lack of evidence for a truly existing difference. Trials should be of a sufficient duration to allow for changes, but especially in populations with schizophrenia, longer duration may be associated with substantial discontinuation rates and thus leads to the question of how best to handle the potential impact of missing data on the estimates of a potential treatment effect.

QoL is not only an outcome but also a factor that may work as a mediator of outcomes: Higher QoL is associated with better treatment adherence, improved community functioning, or lower relapse rates. QoL assessments should thus always be included in trials, even if this is only to more fully characterize the patient population. Baseline differences in QoL measures between patients or sites may lead to different outcomes between sites and could result from differences in sampling, treatment settings, or basic background care for the patients.

In efficacy or effectiveness studies, the inclusion of subjective and objective QoL measures provides important information to clinicians on relevant positive or negative properties of specific compounds that would not be illustrated by classical outcome measures based on recording symptom change. In this respect, any discrepancies between results from patient-rated and clinician-rated instruments should be discussed and explained (e.g., due to different underlying concepts). The guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) on long-term treatment of schizophrenia (Hasan et al. 2013) highlight the relevance of QoL since one of the declared main goals of treatment during the stable phase is to ensure that

the patients are maintaining or improving their level of functioning and quality of life. Psychopharmacological management should be individually tailored to the needs and preferences of the patient, focusing, among others, on improvement of subjective well-being and quality of life. In general, clinicians will benefit from reliable information about the degree with which compounds improve or negatively interfere with aspects of QoL in schizophrenia. So far, based on the available literature, the guideline makes no recommendations for specific treatments as they have found "no evidence that would favor one particular antipsychotic drug or a group."

After the introduction of second-generation antipsychotics, several studies have been conducted that included measures of QoL. With the difficulties in demonstrating superior efficacy versus first-generation compounds, the comparisons eventually focused on safety and tolerability as well as on quality of life. Advantages of the newer drugs were their improved subjective tolerability and a more favorable side-effect profile with respect to extrapyramidal symptoms and neuroleptic dysphoria leading to inquiries of how these differences might translate into improved quality of life. Initially, the target audiences were clinicians (prescribers) and later also agencies involved in pricing and reimbursement, but often the assessment of QoL was not the primary target of the studies. Many of these studies also did not allow for clear conclusions due to significant methodological shortcomings – discussed in more detail by Awad and Voruganti (2004). The authors criticize that "frequently the inclusion of quality of life assessments in clinical trials seems to be an afterthought. Many of the studies are short term lasting only a few weeks with no long-term follow up. The use of several measurement scales based upon different theoretical constructs seems to limit any reliable comparative analysis. Some of the instruments used are of unknown psychometric properties and maybe inappropriate for use in the schizophrenia population or are not sensitive enough to detect small changes in quality of life as expected in such relatively short term trials."

In recent years, studies have been conducted for submissions to Health Technology Assessment (HTA) bodies in order to secure satisfactory pricing and reimbursement for newly introduced compounds. From a HTA perspective, HRQL is one of three important factors (together with mortality and morbidity) for relative effectiveness assessment of new drugs. Both generic HRQL and disease (or population)-specific questionnaires are useful and effects should be investigated in comparative, interventional trials, taking into consideration that the trial conduct itself may influence QoL results ("trial effect"). For cost-utility assessment health gains are normally presented in terms of quality-adjusted life years (QALYs). HRQL findings are then translated into utility and entered into the calculation of the QALY. This process will be greatly facilitated when selecting a HRQL measure, for which a set of preference-based utility values has been elicited. Cost-utility analyses have been successful in various indications, but their applicability to schizophrenia appears to be still a challenge in view of the heterogeneity of the condition and the complex clinical picture. The timing of these studies is still debated. Results from phase II trials may have limited utility for HTA assessments but could provide relevant information for further clinical development and the choice of QoL measures when designing the phase III trials.

As an example for HTA assessments, the National Institute for Health and Care Excellence (NICE) appraises the evidence of all the clinical benefits and costs of an intervention in the broadest sense, including the impact on quality of life. Data on final clinical outcomes such as life years gained and changes in patient quality of life are actually preferred to intermediate clinical outcomes. NICE is primarily interested in "clinical effectiveness" which encompasses benefits to patients including reductions in morbidity and mortality but also improved quality of life. The ideal source of effectiveness data is from prospective, randomized, controlled trials with a naturalistic design and minimal restrictions on the normal decision-making processes of health-care professionals and patients.

Regulatory claims based on health-related quality of life (HRQL) measures are accepted by both the FDA and EMA. While the patients' perspective is gaining importance in clinical research for the EMA and FDA, HR-QoL end points are still playing a minor role in product claims with psychiatry products, possibly due to methodological weaknesses of the trials submitted which have been criticized for an "unscientific practice of including any vaguely relevant PRO instrument in a clinical trial at the eleventh hour" (Speight and Barendse 2010).

Over the years, the FDA also appears to have become more critical of instruments used to measure patient-reported outcomes (PROs) in clinical trials. In 2006 the agency has sent out the draft of a guidance document on patient-reported outcomes which covers assessment of QoL and was finally issued in 2009 (FDA 2009). In 2014 the agency has also provided guidance on the qualification process for drug development tools which describes the framework for how drug developers and manufacturers may submit and seek qualification approval for tools like PROs that may be used for HRQL claims (FDA 2014). After the release of the draft guidance in 2006 on PROs, the number of successful PRO-based product labeling claims has actually fallen compared with the preceding 5 years although the guidance document now outlines a clear strategy for the inclusion of PROs in clinical trials, similar to that for other clinical end points. In order to make valid PRO claims for new compounds, drug companies will need to start collecting evidence in support of the PRO already as early as phases I–II and to carefully consider the development of appropriate PRO measures. According to the FDA, claiming a statistical and meaningful improvement in HRQL implies (1) that all HRQL domains that are important to interpreting change in how the clinical trial's population feels or functions as a result of the targeted disease and its treatment were measured, (2) that a general improvement was demonstrated, and (3) that no decrement was demonstrated in any domain.

The EMA, unlike the FDA, has not issued formal guidelines specific to PROs but has instead published a reflection paper (EMA 2005) to provide broad recommendations on health-related quality of life (HRQL) evaluation in the context of clinical trials. So far, the EMA has been more likely to grant PRO claims and is more likely to grant claims for higher order constructs such as HRQL. The EMA also accepts existing measures, including global assessment and diaries, provided the assessments are supported by peer-reviewed publications covering the development and validity of the instruments. This difference in acceptance rates possibly results from

the way both agencies treat HRQL measures. The EMA recommends specific, validated instruments for use within the therapeutic area, whereas the FDA typically recommends the identification of concepts and does not endorse specific measures.

A paper by Marquis et al. (2011) summarizes the current situation as follows: 15 guidance documents from the FDA and 34 guidance documents from the EMA contain recommendations for the inclusion of PRO end points in clinical trials. However, the FDA referred to HRQL (as a secondary end point) in only 3 guidance documents, whereas the EMA recommended use of HRQL end points in 22 guidance documents. The FDA approved 8 products with PRO end points documenting treatment benefits characterized as HRQL and the EMA approved 16 products with a PRO claim reflecting HRQL data, but none of these HRQL claims were granted in the context of a schizophrenia indication.

With regard to the timing of HRQL assessment in relation to the marketing authorization, the EMA reflection paper on HRQL describes broadly two situations: When the medicinal product has not yet received a marketing authorization, the sponsor company may choose to study the effects on HRQL simultaneously to the efficacy/safety of the medicinal product in pivotal (phase III) trials. Studies should be powered to test both for the efficacy of the test drug versus placebo and/or active comparator as appropriate and for the HRQL change. Efficacy and HRQL are co-primary end points, or alternatively, a hierarchical testing of end points could be applied. When the medicinal product has already obtained a marketing authorization, and if HRQL is planned to be studied once efficacy and safety of the test drug have already been shown in the target population, it may be difficult to perform a study versus placebo. In this case HRQL change due to the test drug may be compared to HRQL change due to an active comparator, and a study incorporating both efficacy and HRQL change (e.g., non-inferiority for efficacy and superiority for HRQL) may be an appropriate design for including data in the label.

A significant limitation is of course that HRQL findings from controlled clinical trials with their structured environment, frequent visits, and more intensive interaction with clinical staff may not be easily transferable to routine practice. Study participants usually have to meet highly selective inclusion and exclusion criteria and their clinical characteristics may vary significantly from those common in routine clinical practice, like higher severity, psychiatric and medical comorbidities, more intensive cognitive impairment, or polypharmacy.

11.3 Some History and then Back to the Future: Quality of Life in Schizophrenia as a Specific Target for Drug Development

Following the initial serendipitous discovery of the first antipsychotic, chlorpromazine, there are now more than 60 first- and second-generation antipsychotics globally available, the vast majority of them already as generics. All antipsychotics are different with respect to their heterogeneous receptor profiles but they are mainly

distinguished by their safety and tolerability, while efficacy differences between them tend to be small in magnitude (except for clozapine which has superior efficacy in treatment-resistant schizophrenia). Antipsychotic drugs primarily target positive symptoms, but there is a significant level of treatment resistance, and many patients do not even respond to clozapine, the only approved drug for this indication. Antipsychotics also have, at best, marginal effects on other, but probably more significant, aspects of the schizophrenia syndrome, as there are negative symptoms, depressive features, and cognitive impairment. In this sense, all available compounds are still only "antipsychotics" and none can yet claim to be an "anti-schizophrenia" treatment although the label claim is usually "for the treatment of schizophrenia."

The choice of positive symptoms as the primary target for treatment has not simply been a consequence of the discovery of chlorpromazine and the development of compounds with a comparable mode of action, but was also due to changes in the concept of schizophrenia over time. When Eugen Bleuler introduced the term "schizophrenia," in his famous monograph from 1911 "Dementia praecox oder Gruppe der Schizophrenien," he stressed that this was not a single entity but a group of disorders sharing a set of basic or fundamental symptoms like loosening of association, blunt or incongruous affect, ambivalence, and autism which he considered unique to schizophrenia. Today, several of the basic symptoms would be identified as negative symptoms or cognitive impairment. Bleuler did not believe that delusions and hallucinations were essential to schizophrenia. In fact, he regarded them as "accessory symptoms" as they more likely represented failed attempts at dealing with the illness.

Kurt Schneider (1959) proposed a new diagnostic approach to schizophrenia based on features that could be more easily identified than Bleuler's basic or fundamental symptoms. The new criteria were restricted to particular types of hallucinations and delusions and have been known as "first rank symptoms." They show improved inter-rater reliability and were integrated into the classification system of DSM-III (American Psychiatric Association 1980). Although Schneider stated that the primacy of first rank symptoms was not a theoretical matter but that they were "primary" only in the practical diagnostic decision making, hallucinations and delusions (also referred to as "positive symptoms") eventually were treated as the core features of schizophrenia. Supported by the specific efficacy of antipsychotic compounds, positive symptoms became the main targets for pharmacotherapy and for drug development. However, a number of meta-analyses have illustrated the important limitations of antipsychotics in the treatment of schizophrenia (Leucht et al. 2009b, 2013). The lack of significant improvements in course and outcome of schizophrenia over the past 100 years for the majority of patients, in spite of the availability of medications, has been discussed extensively (Hegarty et al. 1994; Jääskeläinen et al. 2013).

Even at present, medications for schizophrenia continue to be approved by regulatory agencies based on their antipsychotic efficacy (and safety) that is usually demonstrated in samples with acutely exacerbations. Antipsychotics will certainly remain useful for symptom reduction in many patients and for reducing the risk of

relapse. Their limitations have, however, led to a shift in goal posts. The field is now aiming at remission (Andreasen et al. 2005) and recovery (Andresen et al. 2003; Silverstein and Bellack 2008; Zipursky and Agid 2015). For schizophrenia, complete recovery implies the ability to function in the community, socially and vocationally, as well as being relatively free of disease-related psychopathology. Therefore, QoL can be considered an increasingly important objective for treatment in schizophrenia, since improvements in QoL would be a significant step forward in reaching recovery.

This should stimulate research and drug development and will obviously require novel approaches and targets for treatments that have different or additional pharmacological effects. More focus needs to be placed on aspects like cognitive impairment, negative symptoms and motivational deficits, depressive symptoms, and anxiety as well as comorbid conditions like substance abuse. Unmet medical needs in schizophrenia are still very high and drug development that seeks treatments for better outcomes will probably need to undergo dramatic changes. Many companies have seen this as too risky and too costly and have therefore left the field or terminated their activities of treatments for schizophrenia. But with the movement of consumerism, there are now clear expectations of better therapies also for schizophrenia that will deliver "value for money." This then provides important commercial opportunities for those companies, who continue their development activities and succeed in finding compounds with improved therapeutic activity and low side-effect burden. New compounds should then be tested in well-designed studies with external validity and a focus on QoL so that they can already bridge the "efficacy-effectiveness gap" (Eichler et al. 2011) during clinical development. Although these trials come with an increased cost, they will have more weight with regulators, HTAs, and payers.

With an increasing shift in psychiatric practice from reducing psychotic symptoms to improving quality of life and with an emphasis on evidence-based medicine, quality of life can play a central role and may become a key target for future drug development in schizophrenia.

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